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The Role of Genetic Factors in the Human Face, Jaws and Teeth: A Review

Foreword

When the Reptilia evolved into the Mammalia there were several profound changes that occurred in face, jaws and teeth, but especially in the latter. The dentition went from polyphyodont—many sets of teeth—to diphyodont—but two sets of teeth, deciduous and permanent; it went from homodont—all teeth alike—to heterodont—different types of teeth, i.e. incisors, canine, premolars, molars. With this arose *timing*—when each set and each tooth appeared—and *sequence*—the order of tooth appearance within each set. There arose a *developmental patterning* in the sense that teeth and bone must develop synchronously in order that functional dental interrelationships—occlusion—be facilitated; there arose also the concept of "dental age" as a biological impulse, to be possibly equated with the more basic biological framework of growth-time, "skeletal age". Dental and skeletal age thus partake of a common element in organic growth: progressive and cumulative *maturation.*

The supporting bony structures of the teeth—the rostrum, the snout, the face—did, of course, change too, but not so radically. The anterior teeth (now the incisors) still were related to a transverse vector of force and of growth; the canine (still a haplodont tooth) remained laterally as a corner-tooth, marking the transition between vectors of transversality and sagittality; the posterior teeth (now the milk molars or the premolars and the molars) still were related to a sagittal vector of force and of growth.

In addition to the foregoing changes another was set in motion, that of *anisomerism,* or the reduction in number of bone or tooth elements either by direct loss or by fusion. The number of discrete cranial and facial bones was reduced, and dentally there was progression from the Mammal-like Reptiles $\frac{5\text{–}1\text{–}4\text{–}7}{4\text{–}1\text{–}4\text{–}7}$, to a generalized Mammalian $\frac{3\text{–}1\text{–}3\text{–}4}{3\text{–}1\text{–}3\text{–}4}$, to a generalized Primate $\frac{2\text{–}1\text{–}2\text{–}3}{2\text{–}1\text{–}2\text{–}3}$ (from 66 to 44 to 32 teeth in, say, 200 million years).

Homo sapiens is the heritor of all this: our face, jaws and teeth are, as it were, the battle-grounds upon which this evolutionary war is still being waged. The changes of ontogeny are no less entrenched than those of phylogeny. The human embryonic, foetal and post-natal organism may not traverse the incredible distances of evolutionary change, but in ten lunar pre-natal months, and in twenty post-natal years, a species-linked (and, hence, genetic) pattern unfolds.

It is, therefore, almost fore-ordained that the "Field Theory" enunciated by Butler [12] should be expounded: the tooth genes just about *must* have a morphogenetic gradient that presides over development, position within a quadrant of like teeth, the shape and

size of individiual teeth and of a group of like teeth, and an over-all " patterning" for the functional behaviour of a tooth within a quadrant, a quadrant and its antimere and its functional opposite (e.g. lower incisors vs. upper incisors), and, finally, the reciprocal functional reaction of grouped quadrants, as in total maxillary arch vs. total mandibular arch.

The basic morpho-functional characters of the teeth may, over evolutionary time, show what Moorrees [104] calls intensification, simplification and retention. Examples of the first are shovel-shaped incisors, a large Carabelli's cusp, and hypertaurodontism; of the second are transition from the "Y5" Dryopithecus pattern to the "+4" human pattern, reduction of cusp number in $\overline{\overline{P2}}$ and in $\frac{M1-3}{M1-3}$, and reduction in tooth number, *per se*.

As we translate all of this into genetic terms in the human facio-dental complex, we shall probably not encounter one-gene substitutions. Instead, we shall cope with polygenic traits, those which, as Witkop [141] says, "are influenced to a great extent by environmental factors", e.g. as in many aspects of growth and development, dental caries, and in "common varieties of periodontal disease". Grüneberg [64, 65] has introduced the concept of "quasi-continuous variation", or "threshold characters" into developmental studies of polymorphism. The term is applicable to certain "all-or-none" traits which may occur in a given percentage of the population. When the trait is present it means [79] "that the individual carries a major gene in the homozygous or heterozygous state, or an appropriate polygenic complex". Hunt calls this system a " dystrophic genotype". In addition there is an "epigenetic endowment". This mediates the threshold above which the dystrophic system is penetrant. The dystrophic genotypes probably are a continuous variation in the total population; but in development they show up as all-or-none entities.

It is now pertinent to consider the actual evidence of what is known, or surmised, about the phenotypic expression of facio-dental traits in Man. The stage is set, so to speak, by Gabriel [35] who observed that there "can be no doubt of a genetic pattern for tooth morphology" which extends "to every minute detail", even into root formation.

The Teeth as a Whole

Kraus [85] has summarized apparent hereditary traits in the human dentition as follows:

DEVELOPMENTAL TRAITS

Crown calcification; Time of molar-cusp coalescence; Age and sequence of eruption in deciduous and permanent teeth.

MENSURATIONAL TRAITS

Cusp number; Crown dimensions; relative molar size; Root length: number of roots.

MORPHOLOGICAL TRAITS

Crown patterns: cuspules, crenations, ridges, grooves, pits; total shape; Carabelli's cusp; Shovel-shaped incisors; Fused and/or curved roots; Enamel extensions and nodules; Taurodontism.

ANOMALOUS TRAITS

Supernumerary teeth and/or roots; Congenitally absent teeth; Peg-shaped teeth; Paramolar tubercle of Bolk.

STRUCTORO-FUNCTIONAL TRAITS

Diastemata and/or tremata; Over-bite, over-jet, prodontism; Arch shape and size, upper and lower; Malpositioned and/or rotated teeth.

Since this list was published evidence has accumulated concerning the inheritance mode of many of the traits. The evidence will be scanned as this review moves along.

In addition to the foregoing, Kraus also listed what he considered the heritable traits of the mandibular first premolar (Pm1 or P1):

External lingual groove: scored as absent, one, two grooves.
Sagittal sulcus, mesio-distally between the protoconid and metaconid: scored as interrupted or uninterrupted.
Deuteroconid a–p position: scored as mesial, distal, median.
Lingual cusps, each with independent apex: scored one to five.
Mesial protoconid margin: scored as absent or present.
Central protoconid ridge: scored as bifurcated or non-bifurcated.
Accessory occlusal protoconid ridges: scored as none or as one to five.
Deuteroconid-protoconid relationship: scored as joined and separate or independent deuteroconid.

Horowitz and Osborne [74] studied the teeth of fifty-four pairs of like-sexed adult white American twins. They concluded that "genetically conditioned variations of a highly significant nature occur in eight of the 12 anterior teeth studied. The canine teeth demonstrate a relatively low hereditary component of variability." It was further observed that "sex and symmetry factors appear to play a part in the variation observed in the maxillary left central incisor and the mandibular left canine and lateral teeth".

Dahlberg [18] and Hanihara [67] have studied certain dental traits from a racial viewpoint, suggesting hereditary transmission via racially-entrenched gene complexes. Dahlberg [18] reports on the incidence of rotated maxillary permanent central incisors: lingual rotation is defined as bilateral or unilateral "winging" and straight; labial rotation as unilateral or bilateral "counterwinging". These rotations occur in 22–38 per cent of American Indians of the Southwest, 10 per cent of Japanese, and 3 per cent of American whites of Chicago. Hanihara studied the deciduous crown traits in Japanese-American hybrids and found the Japanese-white, in tooth morphology generally, to be midway between the parental norms, while Japanese-Negro were closer to Japanese norms. Both the Japanese-white and Japanese-Negro are close to Japanese norms in the cusp development of the maxillary first permanent molar, but are nearer the white Americans in Carabelli's cusp development on the maxillary second deciduous molar.

Garn [36] has studied sibling resemblances in deciduous tooth composition as follows:

NO. PAIRS	MEASUREMENT	CORRELATIONS	
		r	Se
12	Ash/dry weight	0·14	±0·28
12	Calcium/dry weight	0·46	±0·23
12	Calcium/ash weight	0·42	±0·24

After observing that "tooth size and mineral mass are largely inherited" he concludes that "the percentage of mineral appears to be inherited too", and that "the calcium/phosphorus ratio is not quite constant, but rather a genetically determined limited variable".

Garn *et al.*[45] report on a study of family-line determinants of dental development. Their findings may be summarized as follows:

1. Buccolingual tooth dimensions show a greater mean percentage of sexual dimorphism than mesiodistal, together with a different rank order of dimorphism percent.

2. The degree of brother-sister dimorphism in canine size shows a higher *r* with dimorphism in adjacent teeth (I2, P1) than with I1, P2, in both maxilla and mandible.

3. Cusp number and mesiodistal diameters are inter-acting polymorphisms in both sexes; this is true of relative cusp number and relative tooth size on M1, M2.

4. Cusp number does not depend on groove pattern (X, Y, +), nor on the strength of expression of Carabelli's cusp.

5. Although they are genetically independent, groove pattern and cusp number "show evidence of simultaneous selection in recent populations".

Tooth Size

With respect to this category, the outstanding researches by far have been carried out by Garn and his colleagues at the Fels Research Institute, Yellow Springs, Ohio, largely on familial and sib-series. Garn, Lewis and Kerewsky [46] studied the X-linked inheritance of tooth size (mesiodistal diameter) in siblings as follows:

TOOTH	SISTER-SISTER CORRELATION		BROTHER-BROTHER CORRELATION		SISTER-BROTHER CORRELATION		RANKING
Maxilla	N	*r*	N	*r*	N	*r*	
I^1	13	0·52	46	0·44	70	0·18	SS>BB>SB
I^2	12	0·65	45	0·06	67	0·14	SS>SB>BB
C	10	0·53	26	0·67	43	0·28	BB>SS>SB
P^1	10	0·66	43	0·59	62	0·19	SS>BB>SB
P^2	7	0·72	39	0·49	49	0·10	SS>BB>SB
M^1	13	0·63	43	0·26	65	0·06	SS>BB>SB
M^2	7	0·82	17	0·19	35	0·27	SS>SB>BB
Mandible							
I_1	13	0·76	42	0·48	65	0·20	SS>BB>SB
I_2	13	0·71	46	0·33	70	0·36	SS>SB>BB
C	9	0·74	38	0·35	62	0·40	SS>SB>BB
P_1	10	0·61	37	0·57	60	0·19	SS>BB>SB
P_2	9	0·55	31	0·46	49	0·27	SS>BB>SB
M_1	10	0·46	45	0·22	60	0·22	SS>BB−SB
M_2	4	0·70	17	0·33	25	0·04	SS>BB>SB
Weighted *r*		0·64		0·38		0·21	

In the foregoing tabulation sister-sister correlations are seen to be highest, followed by brother-brother and sister-brother in order. In thirteen of fourteen teeth compared sister *r*'s exceeded brother *r*'s, and in nine of fourteen brother-brother *r*'s exceeded cross-sex *r*'s. It seems likely that sisters, having the paternal X chromosome in common, "are necessarily more alike in tooth size than brother-brother or sister-brother pairings".

The same authors [47] have studied the size interrelationships of the mesial and distal teeth as shown below (mean *r*'s are given):

TOOTH	CORRELATION WITH ALL OTHER TEETH *	CORRELATION WITH OTHER MORPHOLOGICAL CLASSES	CORRELATION WITH LIKE-NUMBERED TEETH †
	(1)	(2)	(3)
		Maxillary, Left	
I^1	0·53	0·51	0·54
I^2	0·49	0·45	0·41
P^1	0·59	0·55	0·55
P^2	0·55	0·50	0·45
M^1	0·52	0·51	0·54
M^2	0·50	0·47	0·43
		Mandible, Left	
I_1	0·58	0·52	0·53
I_2	0·60	0·54	0·45
P_1	0·59	0·55	0·54
P_2	0·58	0·53	0·50
M_1	0·52	0·52	0·50
M_2	0·43	0·41	0·39

* Isomeres $\underline{1}|$ with $|\underline{1}, \underline{2}|$ with $|\underline{2}$, etc., are excluded.
† I_1 with P_1 and M_1; I_2 with P_2 and M_2, etc.

The more distal teeth show lower communalities than the more mesial teeth, within each morphological class. This was also the case with *r*'s involving the remaining teeth (excluding isomeric pairs), with intraclass *r*'s excluded, so that I's were compared only to P's and M's, and, finally, where like-numbered teeth are compared exclusively *intra se* (columns 1, 2, 3, respectively), in the above tabulation.

Garn, Lewis and Kerewsky [46] have reported on sex differences in tooth size (mesiodistal crown diameter in 243 American white children). The sex size difference is 4 per cent, greatest for permanent canine (6 per cent), least for the permanent incisor group (3 per cent). "The sex difference in tooth size may be taken as an estimate of the magnitude of the chromosomally-determined and presumably Y-influenced size difference, where steroid mediation is not additionally involved."

In an analysis of fields of tooth size the foregoing authors [44] report on various size correlations as follows:

UPPER-LOWER SIZE CORRECTIONS

	Right	*Left*
I1	0·75	0·72
I2	0·59	0·61
C	0·75	0·74
P1	0·75	0·76
P2	0·71	0·64
M1	0·70	0·69
M2	0·58	0·64

INTRA-QUADRANT SIZE CORRELATIONS

	I_1	I_2	C	P_1	P_2	M_1	M_2
I1	—	0·61	0·61	0·57	0·48	0·53	0·40
I2	—	—	0·54	0·50	0·45	0·40	0·36
C	—	—	—	0·63	0·58	0·54	0·51
P1	—	—	—	—	0·74	0·55	0·53
P2	—	—	—	—	—	0·52	0·51
M1	—	—	—	—	—	—	0·52
M2	—	—	—	—	—	—	—

LEFT-RIGHT SIZE CORRELATIONS

	Maxilla	*Mandible*
I1	0·92	0·92
I2	0·91	0·94
C	0·91	0·92
P1	0·92	0·93
P2	0·89	0·90
M1	0·90	0·91
M2	0·83	0·82

Moorrees and Reed [107] have also reported on correlations among the crown diameters of human teeth. Especially important are their observations on deciduous teeth as related to their permanent successors. The correlation between the sum of c, m1, m2 and C, P1, P2 is 0·50 in the maxilla, 0·57 in the mandible. The correlation between I1–2, C and P1, P2, is 0·50 in the maxilla, 0·58 in the mandible. The *r* between the combined crown diameters of the maxillary and mandibular teeth (dm_2-d_1 and P2-I1) is 0·85. The authors conclude that the high *r* of all deciduous and permanent teeth within each jaw (0·57 and 0·61, upper and lower respectively) and between jaws (0·77) "suggest the existence of an over-all [genetic] factor influencing tooth size". It is interesting to note here that the high *r* between upper M1 and m2 (0·51) and lower M1 and m2 (0·53) tends in Moorrees' opinion, to support Bok's contention that M1 belongs to the deciduous dentition.

In a twin study Horowitz, Osborne and De George [74] emphasize that "a comparison of the average of the differences for monozygotic and dizygotic twins will provide a test of the observed effect of a difference in one-half the total hereditary constitution". They studied tooth dimensions in 54 pairs of like-sexed white American adult twins (33 monozygotic, 21 female, 12 male) and 21 dizygotic (16 female, five male); measured were the maximum mesiodistal diameters of $\frac{\text{C I2 I1 I I1 I2 C}}{\text{C I2 I1 I I1 I2 C}}$.

In monozygotic twins the upper and lower left I1 had the smallest mean difference, while the upper left I2 and the lower left C had the greatest mean difference. In dizygotic twins the upper left C and the lower left I2 had the smallest mean difference, while upper right I2 and lower right C had the greatest mean difference. Analysis of variance shows a "strong genetic component of variability" in the four upper and four lower incisor teeth. The canines show much less genetic variability. Environmental variation is twice as great in upper I1–2 as in lower I1–2.

The data to this point serve admirably in support of the "Field Concept". In each morphological group the " key" tooth is the more mesial, i.e. for incisors it is I1, for premolars P1, and for molars M1. These, along with C, are genetically the more stable; by contrast, I2, P2, M2–3, are genetically more variable. There is a sort of "distance gradient" with group mesiality elected as a focal site of stability. Whether this is negatively related to phylogenetic anisomerism is not demonstrable, but one may venture a guess that it is.

Structural Defects in the Teeth

According to Finn [24] there are two classes of hereditary defects in enamel and dentin: (1) those affecting the development and calcification of the teeth either as a separate entity or as part of a syndrome involving other calcifying structures of the body; (2) those involving hereditary metabolic blood disorders or blood antigen, i.e. antibody reactions which cause visible changes in enamel and/or dentin. Witkop [140] makes the categorical statement that "there are five or more distinct genetic entities causing enamel defects".

Finn [24] feels that enamel hypoplasia is due to an autosomal dominant gene, an opinion shared by Shear [131] and Dreyer and Shear.[21] Rushton [125] distinguishes between enamel hypoplasia (enamel agenesis) inherited as a dominant trait, and enamel hypocalcification, also dominant, with no sex difference. Tobias,[137] however, feels that defective enamel may be transmitted either as a simple dominant or as sex-linked. Finn (following Witkop) divides enamel hypocalcification into hypomaturation, a sex-linked trait, and pigmented hypomaturation, possibly an autosomal recessive trait. Witkop [140] reports that in children with cerebral disorders 54 per cent showed enamel hypoplasia, as compared to only 9 per cent in controls.

Dentinogenesis imperfecta, according to Finn, is a simple autosomal recessive trait, with modifying factors but with good penetrance. Hursey *et al.*[80] studied a "racial isolate" of 4,000–5,000 persons (Caucasoid, Negroid, Amerind) and concluded that it "appears to be transmitted as an autosomal dominant trait", but that "wide variations in the manifestation of this trait were observed in patients heterozygous for the dominant gene". Dentinal dysplasia is an autosomal dominant (Finn [24]).

Heys, Blattner and Robinson [71] observed osteogenesis imperfecta and odontogenesis imperfecta in eighteen families, and reported the syndrome to be "genetically dominant, but variable in the degree of expression". Finn also regards the complex as an autosomal dominant. An associated defect here, with normal but incompletely calcified enamel, is opalescent dentine, which Rushton [125] and Tobias [137] regard as a dominant trait.

Other defects, listed by Finn, which may shape up in the teeth, are involved in the following: hereditary vitamin D-resistant rickets, a sex-linked dominant; Fanconis' syndrome, a rare recessive gene (low plasma level of inorganic phosphate, amino acid, glucose phosphate, bicarbonate, and (?) potassium); hypophosphotasia, a recessive trait, with (?) more than one gene (teeth are hypoplastic and tend to exfoliate prematurely); Rh incompatibility, with RH antigen a dominant gene, and a negative individual a homozygous recessive genotype; congenital porphyria (cf. porphyria imperfecta), due to an autosomal dominant gene (teeth, bones pigmented).

Anodontia is part of a syndrome of ectodermal dysplasia (anhidrotic). Greene [60] regards it as a sex-linked recessive, predominantly male. Rushton [125] agrees, but cites Böök who calls it a simple autosomal dominant when associated with absence of P1, P2, prematurely white hair, and excessive sweating of palms and soles. In association with absence of $\underline{I2}$ it behaves as a simple dominant with no sex limitation. McDonald [98] holds that anodontia in hereditary ectodermal dysplasia is incompletely recessive.

Absence of Teeth

Whether or not congenitally absent teeth to-day is a reflection and carry-on of a phylogenetic anisomerism is a moot point. It certainly is a possibility. Dahlberg [17] suggests

a loss tendency—as measured by eruptive variability—in Man as follows (S = stable, V = variable, in terms of an appearance/absence dichotomy; there is no R/L side difference)

S	V+	S	S	V	S	V	V++
I1	I2	C	P1	P2	M1	M2	M3
$\overline{I1}$	$\overline{I2}$	C	P1	P2	M1	M2	$\overline{M3}$
V	S	S	S	V	S	V	V++

The genetics of missing teeth is probably quite complex, for it is apparently tied-in with general systemic development. For example, Keene[8a] points out that children with very high or very low birth weight more frequently have missing teeth, and so do twins.

Here it is obvious that $\frac{M3}{\overline{M3}}$ is the single tooth most frequently absent, with mandibular M3 possibly absent more often than maxillary. Then follows maxillary I2.

Rushton [125] feels that absence of $\overline{I2}$ is a simple dominant, with no sex limitations. Other students feel that the problem is more complex. Lasker [93] notes that $\overline{I2}$ may be peg-shaped, it alone may be absent or it may be accompanied by missing $\overline{I1}$, or in some cases nearly one-half of the other teeth may be absent (oligodontia). Tobias [137] points out that where both $\overline{I2}$ and $\overline{I1}$ are absent it may be of moment that each is at contiguous bony margins (premaxillary-maxillary and mandibular symphysis, resp.). Thomsen [136] reports on her studies on Tristan da Cunha, and finds that missing $\overline{I2}$ is associated with other genetic factors, apparently behaving differentially as dominant, as recessive, as sex-linked. Rantenen [118] observed nine variable patterns of missing and/or peg-shaped $\overline{I2}$ in 2 per cent of 2218 Finns, with no sex differences. Lasker,[93] in commenting upon variability in missing $\overline{I2}$, feels that "the genes responsible . . . are apparently different, despite the fact that the anomalies tend to grade into each other". Schultz [128] merely concludes that there is a "hereditary tendency" for the absence of $\overline{I2}$, with "different genetic modes in different families".

Missing M3 seems to be most common in Mongoloids (Chinese 17–32 per cent, Eskimo 25–28 per cent, Amerind 13 per cent), next in Caucasoids (7–26 per cent, for $\overline{M3}$) and least in Negroids (Amernegro 11 per cent, African Negro 0 per cent, [7, 16, 55, 70] According to the third-cited authors there are upper/lower, R/L differences as seen in an Ohio sample (figures are percentages):

Missing M3	ORTHODONTIC SERIES			FELS SERIES			COMBINED †
	Boys (214)	Girls (262)	Pop.*	Boys (91)	Girls (82)	Pop.*	
Maxillary, R	5·1	9·2	7·1	—	—	—	—
Maxillary, L	5·6	7·2	6·4	—	—	—	—
Mandibular, R	8·4	11·4	9·9	—	—	—	—
Mandibular, L	6·5	12·6	9·5	14·3	11·0	12·7	11·1

* A 103:100 sex ratio is assumed.
† Not weighted for sample size.

It is apparent from the above that $\overline{M3}$ is absent more often than M3, both absent more often in females, and that side difference is equivocal. Adler [2] is in only partial agreement. In eighteen to twenty-one-year-old Germans he found M3 absence in 27·5 per cent males, 27·7 per cent females; in the maxilla the total frequency was 19 per cent, in the mandible 17·4 per cent with maxillary bilaterality 42·86 per cent, mandibular bilaterality 56·31 per cent.

Garn and his associates,[39, 42, 43, 53, 54, 55] have made both intensive and extensive studies of M3 agenesis. When M3 is absent the other teeth are delayed in their calcification and movement, they are often smaller in size, and they are more frequently themselves absent. In M3 agenesis the formation sequence "tends disproportionately" to be P2, M2; where M3 is present the sequence remains M2, P2; further, in the sibs of an M3 agenetic propositus the M3 is delayed in its calcification timing.

The percentage incidence of other missing teeth in conjunction with M3 agenesis, is as follows [39]:

TOOTH	M3 AGENESIS	NORMAL
I1	3·0	—
I2	12·0	1·5
C	1·0	—
P1	1·0	—
P2	11·0	1·5
M1	—	—
M2	3·0	—

The association between presence/absence of M3 and the presence/absence of other teeth gives an $\overline{X}^2$ value of 157·1.

The following summary by Garn, Lewis and Vicinus [54] places M3 agenesis in a genetic context:

> Third molar agenesis is a relatively common polymorphism occurring in 16 per cent of the southwestern Ohio white population. Though previously treated as an independent anomaly, this number reduction is unquestionably related to agenesis of other teeth, to delayed formation timing of the remaining posterior teeth, to differences in tooth sequence polymorphisms, and to delayed timing and movement of the third molar tooth itself in the siblings of affected individuals. The association between third molar agenesis and reduction in the number of other teeth fits the hypothesis of a field of variable intensity, which, in its greatest degree of expression, eliminates all four third molar teeth and a maximum number of other teeth. The association between third molar reduction and developmental delay in the dentition is susceptible to at least two hypotheses, one involving pleiotropic manifestations of a single gene and the other involving two independent genes, the first favouring developmental suppression and the second affecting formation timing. While the degree of independence between these two phenomena may show which hypothesis is correct, the possibility of closely linked genes must also be considered. In this latter event, the monogenic and polygenic hypotheses would be operationally identical.

The oft-advanced hypothesis that tooth absence is a correlate of jaw-size reduction is rejected by Brothwell, Carbonell and Goose [10]: "There are certainly no good grounds for believing that an increase in hypodontia in *Homo sapiens* is purely associated with the trend toward smaller jaws".

Tooth Calcification and Eruption

Here we shall adopt the generally accepted stages: *calcification*: (*a*) initial; (*b*) beginning of root formation; (*c*) apical closure; *eruption*: (*a*) alveolar, (*b*) attainment of occlusal level.

Kraus [86] has studied the four deciduous molars and reports that each "shows clear-cut distinctions in both sequence and patterns of calcification", and that "together they

form a quite integrated pattern of molar development." He observes that it "would . . . appear reasonable to assume that the molar calcification process is under rather rigid genetic control", but that "how this control is mediated can not yet be answered".

Moorrees [105] and Moorrees and Reed [107] have evaluated tooth emergence and eruption in relation to dental arch growth. It was found for 184 individuals (observed between three to five and sixteen to eighteen years) that "tooth emergence and eruption are more suitable as parameters of dental development than chronologic age in defining the changes in arch dimension . . .". In this sense, therefore, tooth eruption becomes a measure of biologic age.

Garn and Lewis [38] have analysed the relationship between the sequences of calcification and of eruption in lower premolars and molars. Their sample was sixteen boys, twenty girls, who were either P2M2 or M2P2 in calcification sequence and either P2M2 or M2P2 in eruption sequence:

FORMATION SEQUENCE		ERUPTION SEQUENCE	
		P2M2	M2P2
P2M2	22	21	1
M2P2	14	7	7

From the above tabulation it is seen that twenty-one of the twenty-two with P2M2 formation sequence went on to P2M2 eruption sequence; seven of the fourteen M2P2 formation sequence shifted to the P2M2 eruption sequence.

Agenesis of M3 has a noticeable effect on the timing of tooth formation, according to Garn, Lewis and Bonne.[41]:

	$\overline{P1}$		$\overline{P2}$		$\overline{M1}$		$\overline{M2}$		$\overline{M3}$	
Group	N	T	N	T	N	T	N	T	N	T
Affected	21	53	20	54	18	52	21	59	—	—
Sibs	22	56	20	53	17	52	24	52	24	57
Control	111	48	118	49	81	48	126	48	125	49

T = normalized sex-specific T-scores for beginning tooth formation, especially cusp formation.

Where $\overline{M3}$ is absent P and M show late formation in both affected and in sibs. In $\overline{M3}$ agenesis the formation sequence was P2M2 = 60 per cent, but in controls only 22 per cent. Hence $\overline{M3}$ agenesis and P2M2/M2P2 sequence polymorphisms are in positive association, and the $\overline{M3}$ polymorphism "may be viewed as the extreme degree of expression of factors delaying tooth formation over a long developmental period", ranging from the first month of life ($\overline{M1}$) to the eighth year or beyond ($\overline{M3}$).

Sibling relationships have been more intensively studied by Garn, Lewis and Polachek,[49] in sixty-two nuclear Ohio families, with 175 sibling pairings (which includes two sets of triplets). Members of a sibship are more alike than by chance alone. For fifty-three correlations twenty-three differed significantly from zero at the 5 per cent level. In boys sib r's averaged 0·29 in girls 0·51; all pairings (B-B, S-S, B-S) for all stages of tooth development had a pooled r of 0·28. There was no difference in the r for calcification and the r for movement, nor did the r differ in earlier or later calcification stages. In the triplets (two monozygotic, one dizygotic) the r in the pair was 0·95, in the single 0·25. "The rate of tooth development is largely, though not entirely, under genetic control, in the absence of endocrinopathy or chromosomal aberration."

In another study the same authors [50] present interrelationships within the dentition:

GROUPING	NUMBER OF CORRELATIONS	CORRELATIONS
Tooth calcif./tooth calcif.	145	0·46
Tooth move./tooth move.	52	0·56
Tooth calcif./tooth move.	104	0·30
Intratooth	11	0·60
Intertooth	67	0·45
Intraclass	36	0·55
Interclass	42	0·40
Intrastage	22	0·57
Interstage	56	0·42

The timing of the formation of M3 has some bearing on its emergence (Garn *et al.*[42]). If it forms *early* then it emerges early and without trouble to the occlusal plane; if *late* then its emergence is slow and troubled (often "impacted").

Grøn [62] reported on the prediction of tooth emergence in 874 healthy white American children (434 M, 440 F). The Greulich and Pyle hand X-ray film *Atlas* was used. Tooth formation stages (P2) were 1/4, 1/2, 3/4, 4/4 root length with open apex. Most teeth observed had 3/4 root formation at the time of clinical emergence. It was concluded that "tooth emergence is more closely associated with the stage of root formation than with chronological age (C.A.) or skeletal age (S.A.)".

Dental Development and Bodily Growth and Maturation

It is generally accepted that tooth formation and eruption are evidences of, and are governed by, growth-timing, i.e. they are basic biologic phenomena, just as are all traits of skeletal development. It is customary, then, to speak of "skeletal age" and "dental age" as biological concepts and, hence, as biological correlates. Tanner [135] states this succinctly:

> Evidently there is some general factor of bodily maturity throughout growth, creating a tendency for a child to be advanced or retarded as a whole; in the percentage attained of his eventual size, in his skeletal ossification, in at least some elements of his permanent dentition. . . .

Garn and Rohmann [51] present general data on X-linked inheritance of developmental timing in Man:

	SISTER-SISTER		BROTHER-BROTHER		BROTHER-SISTER	
CHARACTER	N	*r*	N	*r*	N	*r*
Ossification rate	494	0·62	688	0·39	1223	0·40
Ossification timing	854	0·54	1200	0·40	2171	0·47
Tooth calcification	140	0·41	246	0·22	486	0·24

The relation between these biological measures has been investigated by Garn, Lewis and Bonne.[42] (See also Garn Lewis and Kerewsky [44]; Garn and Rohmann.[52] In the first-named study results are as on p. 176.

For M_2 the *r*'s average 0·3 higher than *r*'s for M_3. Of this, the authors conclude that "interrelationships with somatic growth and sexual maturation were low and rarely significant, thus emphasizing the developmental autonomy of the third molar tooth". The 1965 study permitted a more general conclusion: "Correlations between maturational status and tooth formation and movement timing are in the expected direction, though

low, rising to moderate levels of *r* at the time of puberty, suggesting direct influence of steroidal hormones on tooth movement of P_2 and M_2".

	M_2		M_3	
CORRELATED PHENOMENA	N	*r*	N	*r*
Menarche, beginning root	63	0·34	38	0·05
Menarche, alveolar eruption	35	0·62	33	0·20
Menarche, cusp level	35	0·61	75	0·06
Menarche, apical completion	15	0·29	12	0·13
Tibial union,* beginning root	101	0·27	48	0·39
Tibial union, alveolar eruption	45	0·51	63	0·28
Tibial union, cusp level	26	0·54	39	−0·07
Tibial union, apical completion	28	0·34	26	−0·01
Hand union,† beginning root	82	0·52	35	0·27
Hand union, alveolar eruption	30	0·57	49	0·17
Hand union, cusp level	17	0·52	29	0·01
Hand union, apical completion	20	0·34	23	−0·21

* Age at completion prox. tibial epiphysis
† Age at complete union digital epiphyses.

Cleft Palate (± Cleft Lip)

The total frequency of this condition per 1,000 births is higher in whites (American, European, 0·80–1·66, av. 1·27) than in Negroes (American, 0·55) (Snodgrasse [133]). Gorlin and Pindborg [57] give an over-all incidence of cleft lip (±cleft palate) of 1:1,000. The incidence is higher in Japanese, lower in American Negro, compared to whites. Cleft palate alone, they say, has a frequency as in cleft lip.

There are several rather extensive earlier studies of the inheritance of lip- and palate-clefting: Fogh-Anderson [26] on Danes, Oldfield [111] on English, Snodgrasse [133] on American whites. Fogh-Anderson held in 1942 [26] that clefting of lip and palate is genetically independent of the isolated cleft palate, and that the first two are heritable anomalies. He stated that there is conditioned or incomplete dominance, with sex limitations to males, and reduced penetrance. In most genetic milieus the gene responsible behaves as a recessive. Isolated cleft palate is rarely inherited as a simple dominant, with sex limitation to the female and reduced penetrance. Snodgrasse suggests a simple recessive heredity with variable expressivity. In a later report Fogh-Anderson [27] stated that cleft lip (with or without associated cleft palate) occurs more often in males; it is most frequently inherited as a recessive trait, so-called "conditioned dominance": cleft palate, alone, is most frequently found in females, inherited in "a smaller number of cases and then as a dominant character with failing manifestation" [reduced penetrance].*

Carter [14] felt that cleft palate is due to "a dominant gene of incomplete manifestation". In speaking of cleft lip (±cleft palate) he felt that "a recessive major gene might be concerned in the etiology". In tabular form may be observed the proportion affected among

* In this review I have not gone into comparative data, but here I make an exception. Fraser [30] feels that the genetic constitution is a factor where, in mice, the pregnant female is given cortisone (standard dose, beginning eleven days after insemination). Cleft palate was produced in almost all embryos of the A/Jax strain, but in only 17 per cent of strain C57BL/6 embryos. "Thus even when a specific environmental agent can be shown to cause malformation, whether it actually does so in a particular case depends partly on the genetic constitution." In further experiments A/Jax female x C57BL/6 male was similarly given cortisone: 43 per cent of the offspring had cleft palate. Then, he tested C57BL/6 female X A/Jax male; only 4 per cent of the offspring had cleft palate. Hence, *both* maternal and foetal genotypes are factors in cortisone-induced cleft palate.

relatives of 291 index patients with cleft lip (±cleft palate), compared with the incidence in the population generally:

DEGREE OF RELATIONSHIP		FREQUENCY		RATIO
		Absolute	Per cent.	
1°	Brother+Sister	27/774	3·5(±0·7)	X35
	Sons+Daughters	21/563	3·7(±0·8)	X35
2°	Uncles+Aunts	15/2504	0·6(±0·2)	X6
	Nephews+Nieces	7/1205	0·7(±0·3)	X6
3°	First Cousins	7/3517	0·2(±0·1)	X2

The decrease from X35 to X6, from 1° to 2°, is a "necessary consequence of a multifactorial hypothesis". The mode of action, says Carter, of a genetic predisposing factor is that there is reduced what Waddington calls "the canalization of development"; as a result the embryo is more susceptible to minor and even haphazard swings in the intrauterine environment.

Fukuhara and Saito [32, 33] feel that cleft palate with cleft lip "may be presumed the most likely manner of 'dominant inheritance' in about more than 50 per cent of the cases". Of palate cleft ("bone cleft") alone they feel that it is "transmitted in the way of dominant inheritance". Their findings are only tentative, for sample sizes are very small.

Lip/palate clefting is often part of a more generalized syndromic defect-pattern, either localized (associated facio-dental structures) or generalized (other bodily organs/systems). Fukuhara and Saito [33] note "microforms" of cleft lip/palate: rotation and crowding of upper anterior teeth; congenital absence of upper I2, I1; asymmetric shape of nose; raphe in upper lip. Kraus, Kitamura and Ooe [90] and Kitamura and Kraus [82] reported on malformations associated with cleft lip and palate in human embryos and foetuses. In the sixty cleft specimens 61·7 per cent had associated malformations, as compared to an average of 25 per cent "reported in the literature". The most common associated malformations were brachydactyly (30 per cent) and syndactyly (25 per cent); other "quite frequently found" malformations are club feet/hands, imperforate anus, absence of genitals and "various skeletal dysplasias".

There is a direct and significant relation between type of clefting and associated malformations:

CLEFT TYPE	WITH ASSOC. MALFORMATIONS	WITHOUT ASSOC. MALFORMATIONS	NO.
I	5	1	6
II	19	19	38
III	14	2	16

($X^2 = 0{\cdot}902$; P = $<0{\cdot}02$, $>0{\cdot}01$.)

In a study of dental models of 105 cleft and 87 non-cleft individuals, plus the tooth buds in ten human foetuses, Jordan, Kraus and Neptune [81] have noted the dental and bodily defects occurring in cases of clefting. It is concluded that "neither the cleft itself nor the type of cleft is an etiological factor in the occurrence of morphological abnormalities in the individual dental units. It would appear that the development of the dentition along with that of the other organs and structures of the body may be affected by the same etiological factor or factors that are responsible for the cleft lip and/or palate". The factor(s) operate in an "apparent haphazard manner" and "it is quite obvious that the picture is not that of an hereditary syndrome".

Woolf, Woolf and Broadbent [145] do not agree. In a study of 10,000 live births in Salt Lake City they felt that both cleft lip and cleft lip with cleft palate have a genetic component in common.

Other studies [30] suggest that cleft lip and cleft of the primary bony palate (in front of the nasopalatine formation) may be genetically mediated, while cleft of the secondary bony palate (behind the nasopalatine foramen) is most often associated with a teratogenic agent during the first trimester. However, it is perhaps better to err on the conservative side and conclude that the dichotomy between primary and secondary cleft palate is not clear-cut. Both may be mediated by genetic factors; less clearly, teratogenic agents may likewise play a role in both, but certainly in secondary.

Dental Caries

Rushton [125] very conservatively says that "there is no satisfactory evidence that susceptibility to dental caries in Man is affected by genetic factors, although it is likely that that is the case". * Grahnen [59] set up two family-groups: A (caries-free propositi); and C (control propositi). He reports that parents and sibs in the A group have a lower DMF index. There was no correlation between fathers and mothers in either the A or C group, nor was there a correlation between parents and children. Between sibs in C, but not in A, there was a significant correlation. Grahnen feels that twin studies demonstrate that genetic factors contribute to individual variability in caries susceptibility. Identical twins are not identical in the distribution of dental caries, but they have fewer differences than fraternal twins, and fraternal twins than siblings or unrelated. Caries susceptibility is concluded to be polygenic.

Tooth-Bone Structure and Function

Under this rubric I shall cover two main classes of data: (1) Morphological traits in the teeth and in the jaws; (2) Inter-related facio-dental "patterns".

In the teeth must be noted "shovel-shaped" incisors, so-called because of an extra marginal enamel ridge on the lingual surface of the incisors, notably upper I1 and/or I2. Accompanying the shovel shaping may be labial lateral ridges, labial axial grooves, and rounding of I2. The condition occurs most frequently among the Mongoloids.[13, 16, 76] Abrahams [1] reported on shovel-shaping in S. Africa, and stated to the condition to be recessive. Riesenfeld [121] surveyed shovel-shaping as follows:

> A previously assumed Mongoloid cline from Indonesia, through Micronesia, to Polynesia, is confirmed by a west-to-east cline in the frequency of shovel-shaped incisors and rounded laterals. Such a cline, and the fact that shovel-shaped incisors

* Caries susceptibility/resistance is almost certainly hereditary in infra-human Mammalia. Rosen, Hunt and Hoppert [122] have demonstrated this in rats. Newly born caries-resistant rats were fostered by caries-susceptible females and vice versa. There was no change in the birth caries-status of the young rats. "The foster mothers did not affect the caries experience of the young they nursed. It may be . . . in these animals the genotype played a role in their resistance or susceptibility to dental caries."

NEWBORN STRAIN	NURSE STRAIN	NO.	CARIES AGE (DAYS)		
			M	S.D.	Range
Susceptible	Susceptible	38	65	2·3	45–111
Susceptible	Resistant	45	64	1·2	55– 84
Resistant	Resistant	37	297	15	176–535
Resistant	Susceptible	39	341	17	164–651

are much more frequent among American Indians than even in the western Pacific, is incompatible with Heyerdahl's claim of an American origin for the Polynesians.

Carabelli's (fifth) cusp, fifth lobe, mesiolingual elevation, Carabelli's tubercle on the upper M1 (though Shapiro [130] says it may be found on m1–2 and M2–3) is another dental trait which has been studied. It is an enamel elevation on the lingual side of the mesiolingual cusp, about halfway between its summit and the neck of the tooth. Its size and the groove that delineates it are extremely variable. Pedersen [114] has summarized its ethnic frequency, ranging on M1 from about 14 per cent in Caucasoids to 23 per cent in Oceanic peoples. In a sample of 200 molars in Iowa children aged nine years, Meredith and Hixon [101] found the cusp to be moderate to large in 60 per cent, absent in 16 per cent. In 70 per cent there was an R/L side difference. Kraus [84] studied eight family histories of the trait, and postulated "a genetic interpretation, based upon the assumption of two allelic autosomal genes without dominance, or, in other words, with 'intermediate' dominance in heterozygotes". He set up three phenotypes: *cc*, complete absence of the trait; CC, full expression of the trait; Cc, variable and less expression of the trait.

The paramolar tubercle of Bolk, also called by Dahlberg [16] "protostylid" in lower molars, "parastyle" in upper molars, and "upper paramolar structures" by Kustaloglu,[92] is derived from the cingulum. It is found on the buccal surface of upper and lower molars, and is most frequently unilateral. It is essentially a Mongoloid trait.

In the maxilla and especially the mandible are tori, respectively torus palatinus and torus mandibularis. Lasker [93] regards the former as possibly due to an autosomal dominant gene. The mandibular torus—a bony outgrowth on the lingual surface of corpus mandibularis—has been intensively investigated by Drennan,[20] Grimm,[61] Hooton,[73] Schreiner,[127] and Weidenreich.[139] Drennan, on 100 mandibles, locates the a-p position of the torus as follows:

	$\overline{I1}$	$\overline{I2}$	$\overline{C}$	$\overline{P1}$	$\overline{P2}$	$\overline{M1}$	$\overline{M2}$	$\overline{M3}$
Ant. limit	1	4	58	24	7	1	3	2
Post. limit	—	—	—	9	43	25	10	13

The trait is by far more frequent in Mongoloids. It may be either a rounded or an elongated (striated) elevation.

Garn, Lewis and Vicinus [54] studied the inheritance of mandibular symphyseal size during growth of Ohio children (sample = 258 adults, 177 children followed serially from eight to sixteen years of age). The symphysis was measured on lateral X-ray films of the jaws. There were set up two categories each of height (high = over 33·1 mm. in M, 29·1 mm. in F, low = below these dimensions in M and F) and thickness (thick = over 14·2 mm. in M, 13·1 mm. in F, thin = below these dimensions in M and F). It was found that mandibular symphyseal height and thickness were independent of bodily height, bodily size and build, tooth size, arch width, and each other. If H = height, h = low, T = thick, t = thin, children of H × H, H × h, h × h matings were "consistently different" during growth; this was also true in T × T, T × t, t × t matings. "The data suggested genetic simplicity for both symphyseal height and thickness and the possibility of Mendelian inheritance of symphyseal thickness."

For over-all face dimensions the best data are those by Osborne and De George.[113] For facial breadth (bizygomatic) there was found a weak hereditary component of variability in males, while in females it was a good measure of hereditary variability. For mandibular breadth (bigonial) the "inheritance factor is good in both sexes". For mouth

breadth there is a "greater hereditary component of variability in females than in males". A resume of these and a few other dimensions is as follows:

DIMENSION	G+E		G only		E only		Sex influence		Size difference	
	♂	♀	♂	♀	♂	♀	MZ	DZ	♂	♀
Total face height	—	×	—	—	—	—	—	—	—	—
Upper face height	—	—	×	×	—	—	—	—	—	—
Nose height	—	—	×	×	—	—	—	—	—	—
Face breadth	—	—	—	×	×	—	×	—	—	—
Nose breadth				×	×	—	—	—	×	—
Mand. breadth	—	—	×	×	—	—	—	—	—	×
Mouth width	—	×	—	—	—	—	—	—	×	×

G = genetic.
E = environment.
× = present as factor.
— = absent as factor.

Meredith [100] studied the age-prediction in nose height and bigonial breadth. He found that incremental growth in nose height from five to seven years was not correlated with increment from eight to twelve years. Bigonial breadth showed an equally poor correlation. Hunt [79] and Moorrees, Fanning and Hunt [108, 109] studied mid-facial dimensions during growth in Boston children. They found that the a-p (depth) growth of the face has some individual predictability in middle childhood, but breadths and heights do not. Genes which preside over facial development, form, and funtion are independent. "The poorer control of the dentition, and of facial heights and breadths, may well account for the frequency with which occlusion deteriorates in middle childhood".

Gaard [34] feels that hypertelorism (incidence 1/100,000) may represent an hereditary factor. The condition is very broad interocular width due to excessive growth of ala parva sphenoidalis. It is, he says, primary—and not a secondary—to facial or nasal clefts, frontal meningocoele, encephalocoele, "or any cranial dysostosis", (See Gorlin and Pindborg [57].)

Cranio-facial Features

Turning now to morphology rather than morphometry of the face, we may first note a seven-generation study by Lebow and Sawin,[94] who noted long vs. round faces, ear prominence, traits of the nose, and cleft of the chin. It was felt that long faces were dominant, due to the "fortuitous recombination" of many genes. The most thorough study of facial features is that Pfannenstiel [115] in Swiss, of three Cantons (203 M, 208 F, aged five to sixty-eight years). Observations are: (1) Chin height, integumental upper and lower lip height, and upper and lower mucous (vermilion) height are due to multiple genes, with no dominance; (2) A thick "swollen" integumental lower lip (often everted) is dominant ("the Hapsburg lip") and there is some relation to prodontia; (3) A median depression of the integumental lower lip (a vertical sulcus, or "cleft chin"), and a horizontal chin groove (sulcus mentolabialis) are simple dominants; (4) In the integumental lower lip (on the chin) there is often a rounded eminence, plus bilateral tubercles, which are genetically related, probably via an autosomal gene with reduced penetrance; (5) In twin studies smaller chin grooves—vertical and horizontal—are simple autosomal dominants, the former with 100 per cent penetrance, the latter with reduced penetrance; (6) Philtrum size and shape (narrow/broad, deep/shallow) seem to be genetically controlled (recessive?); (7) Mouth breadth, as proportionate to total lip height, to total face height, and to bigonal breadth, evinces no definite evidence of genetic mediation.

In the 1940s rather extravagant claims for genetic specificity in the dentofacial

complex were made by Hughes,[77] Hughes and Moore,[78] Moore [102] and Moore and Hughes.[103] Familial heredity was asserted for jaw "displacements", tooth inclination, asymmetry or lateral displacement of chin or gonial area, asymmetry in orbital level, in a-p malar position, in dental arches, in ramal height, in corporal length, and in upper and lower dental heights, differences in absolute size of ramus, corpus, palate height and width, and Frankfort Horizontal/occlusal plane angle. In the 1941 article it is stated that "probably 85–90 per cent of the variability in both the deciduous and permanent dentitions can be ascribed to heredity". Hughes takes himself "off the hook" somewhat when he observes that "most of the cranio-facial features, attribute as well as measurement, appear to be multiple factor traits. Single genes segregating normally seem to be the exception rather than the rule. Likewise, completely dominant genes and their recessive alleles are poorly represented." Rubbrecht [123] stated that mandibular prognathism and maxillary retrognathism are inherited as irregular dominants, and that "the shape and size of the jaws are in great measure determined by heredity".

In 1888 Kingsley (cited by Horowitz, Osborne and De George),[74] observed that "the cause of irregularities of the teeth is . . . sometimes due to the inheritance of large teeth out of all proportions to the size of the inherited jaw". This early statement is sufficient to set the stage for a current look at what is known about facio-dental relationships as a whole. Goodman [56] feels that "from the study of twins, pedigrees, and populations [there is] ample evidence to support the generalization that genetic factors participate in every aspect of dentofacial development".

This conclusion is buffered not only by studies of normal individuals (as in twins, family-lines, and so on) but even more clearly in syndromes of facio-dental defect. Thus, Gorlin, Redman and Shapiro [58] (see also Gorlin and Pindborg [57]) have studied the effect of X-chromosome aneuploidy on jaw growth. The number of X chromosomes influences palatal form, "the palate becoming progressively shallower with the addition of each X chromosome". The Y chromosome has a similar effect, though less marked. The XXY subject has a prognathic profile, with teeth in Class I occlusion. The XO subjects tend to have a retrognathic mid and lower face, while the XXY subject has a prognathic mid and lower face. In the XXXXY syndrome there is marked prognathism, heightened at puberty.

Ruess, Pruzansky and Lis [124] and Aduss and Pruzansky [3] have studied the "oral-facial-digital" Syndrome (OFD) which is a multiple congenital condition in females with associated chromosomal anomalies. Pertinent to this review are: (1) Facial traits, as shortened alar cartilage and columella, median defect of upper lip, through the vermilion border, frequent hypertelorism; (2) Oral cavity traits, as submucous bilateral cleft of the primary and secondary palate, asymmetrical cleft of the soft palate, enamel hypoplasia of varying degrees, tendency to high caries rate. The condition is due to partial trisomy "for a specific chromosomal segment" (two OFD patients, mother and daughter, "have an insertion in one No. 1 chromosome"). In OFD children the cranial base angle (basion to sella to nasion *) is greater than normal, i.e. it increases; the mandible is dysplastic, the position of the hyoid relative to the mandibular symphysis is altered and in OFD total facial height is less.

Altemus [4] studied the incidence of cephalo-facial birth defects generally and found racial (American Negroes and Whites) and geographic differences. The probable underlying variable is the socio-economic milieu.

Crigler, Cohen and Wittenborg [15] point to the hypoplasia of maxilla and mandible found in the Treacher-Collins Syndrome. They note also that "dental maturation" (dental

* Basion is in midline of anterior margin of foramen magnum, sella is midpoint of outline of sella turcica, nasion is midline junction of internasal and naso-frontal suture.

age) seems to be independent of accelerant or decelerant changes (usually endocrinic) in "skeletal maturation" (skeletal age).

The problem of *Syndromes* must now be considered. Some congenital syndromes are non-genetic, e.g. thalidomide and rubella. Others are genetic and it is these that are worthy

TABLE 1

Aberrations of cranio-facial skeleton and of the teeth in syndromes
(from Falls [23])

SYNDROME	SKULL	FACE	TEETH
Aperts [1]	Acrobrachycephaly	Hypertelorism Hypoplastic maxilla Bifid uvula, post cleft palate in 25 per cent	Hypoplastic Malocclusion Crowded teeth
Crouzon [2]	Premature sutural synostosis, resulting in anomalous cranial shapes	Hypoplastic maxilla Hypertelorism Shallow orbits Mandibular prognathism Ogival palate	Malocclusion Abnormal spacing
Franceschetti [3]	—	Hypoplastic malars Hypoplastic mandible Abnormal TMJ	Malposition Accessory teeth Partial anodontia Caries Malocclusion, and often il at birth
Otomandibular Dyostosis	—	(Most often unilateral) Mandibular agenesis-angle and ramus Malformed TMJ Asymmetry Cleft palate Facial clefts	Irregularities in position Abnormalities in size and shape
Hallerman-Streif	Brachyscaphocephaly Fontanelles close late, or remain open	Mandibular hypoplasia Maxillary hypoplasia Ogival palate	Accessory teeth Often il at birth Malocclusion Caries
Pierre Robin [4]	Frequent platybasia	Mandibular hypoplasia Cleft palate	Malocclusion Malposition
Cleidocranial Dyostosis	Prominent frontal and parietal bosses Membranous bones poorly ossified Fontanelles close late or remain open	Partial aplasia, bones of face Maxillae aplastic Ogival palate	Eruption late Malposition in 50 per cent Caries Exfoliation deciduous delayed
Marshall	Frontals thick Frontal bossing Frontals large	Hypoplastic nasals Hypoplastic maxillae Hypertelorism (mild) Thick, curved lips	Partial anodontia
Arrhinocephaly Unilateralis [5]	Frontal defective Cribriform plate absent	Defective nasals, ethmoid Cleft palate	Maxillary teeth malposed

[1] Acrocephalosyndactylia.
[2] Craniofacial Dysostosis.
[3] Manidbulofacial Dysostosis.
[4] Also called Micrognathia, Glossoptosis Syndrome; is part of first visceral arch syndrome.
[5] Basically a disturbance in the closure of the maxillary and nasolacrimal processes; Cyclopia is a more severe degree of this failure.

of note. McKusick [99] states that there are "at least four types of genetic change producing syndromes"; (1) Mutation in a single structural gene; (2) Mutation in two or more closely linked genes, not yet separated by crossing-over ("no convincing example in Man is known"); (3) Mutation in an operator gene "controlling the function of the structure

genes in the operon" (an operon is "two or more closely linked structure genes"); (4) Chromosomal aberrations.

A useful tabulation of dento-facial traits in various syndromes is that of Falls.[23] Pertinent osteo-dental aberrations have been selected by me and are in Table 1. Falls feels that Apert's Syndrome is an irregular dominant with recessive transmission of the trait; Crouzon's Syndrome is an irregular and regular autosomal dominant trait, ±recessive autosomal trait; Franceschettis Syndrome is an irregular dominant trait; the genetics of Otomandibular Dyostosis is not known, as is true of Hallerman-Streiff's Syndrome; a genetic basis for Pierre Robin's Syndrome is "not proven"; Cleidocranial Dyostosis is an autosomal dominant trait with "excellent penetrance"; Marshall's syndrome is a dominant autosomal trait, with "good penetrance"; the genetics of Arrhinencephaly Unilateralis is unknown (may be tied-in with heart, anal and visceral defects).

By far the most complete study of syndromic involvement of cephalo-facial-oro-dental structures is that of Gorlin and Pindborg.[57] In Table 2 is outlined the more common such Syndromes. As in Table 1, I have selected only osteo-odontological traits of skull, face and teeth. The authors do not, for the majority of Syndromes, assay a definitive statement on hereditary mechanism. The syndromic association may imply a timing-complex, i.e. embryogenetic timing, or may imply the possibility of genic and/or chromosomal involvement. For the purposes of this review it is sufficient that there is an involvement of jaws and teeth as part of a more general syndrome of effect.

TABLE 2

Aberrations of cranio-facial skeleton and the teeth in syndromes
(from Gorlin and Pindborg [57])

SYNDROME	SKULL	FACE	TEETH
Bird-headed Dwarf (Seckel) [1]	Small cranial circ.	Small mandible Occ. high-arch palate	Occ. hypodontia Mal-alignment Enamel hypoplasia Maloccl. (II, 1)
Ellis-Van Crevold Syndrome [2]	—	—	Natal teeth 25 per cent Hypodontia, espec. lower anteriors Microdontia Irreg. spacing Late eruption Molar crowns irreg. shape Occ. enamel hypoplasia
Trisomy 21 [3]	Freq. brachycephaly	Depressed nasal root	I2 abs. 25 per cent, or peg-shaped Hypodontia in 50 per cent Late eruption in 75 per cent
XO Syndrome [4]	Asymmetry	Asymmetry	Premature eruption Crowding Short roots
XXY Syndrome [5]	—	Mand. prognathism ++ Palate wide, flat	—
Lateral Facial Cleft	—	Micrognathia	Supernumerary occ.
Medial Facial Cleft	—	Hypertelorism	—
(Pierre) Robin Syndrome [6]	Occ. hydro- or microcephaly	Micrognathia Palate high arch Occ. cleft palate up to 1/3 hard palate	—
Cleidocranial Dyostosis	Brachycephalic, large skull Prominent bossing Fontanelles close late	—	—
Craniocarpotarsal Dystrophy [7]	Steep ant. cranial base	High, arched palate	—

TABLE 2—*continued*

SYNDROME	SKULL	FACE	TEETH
Craniofacial Dyostosis [8]	Frontal bosses ++ Brachycephalic Tendency to C, S, L early closure	Hypertelorism Hypoplastic maxilla Palate V-shaped Palate high, short	Crowding Cross-bite ++ Partial anodontia Peg teeth common
Sturge-Weber Syndrome [9]	—	Occ. high arch palate Hypoplastic jaw on affected side	Eruption of perm. irreg. (early or late)
Hurler's Syndrome [10]	TMJ less mobile	—	Microdontia Short Peg-shaped Wide spaced Malocclusion
Hypertelorism [11]	Brachycephalic	High arch palate Often cleft palate+cleft lip	I2 often absent Occ. microdontia Occ. amelogenesis

$$\text{Canthal Index (CI)} = \frac{\text{medial canthus diam.}}{\text{lateral canthic diam.}} \times 100$$

$$\text{Circumference-interorbital Index (CII)} = \frac{\text{interorbital diam. (med. canthic/}}{\text{head circumference}} \times 100$$

CONDITION	CI	CII
Upper limit, normal	38–	6·8–
Europia	38–42	6·8–8·0
Hypertelorism	42+	8·0+

Hypodontia Mesoectodermal [12]	—	Pal. occ. high ++ Premaxilla rel. small	Hypodontia (anodontia rare) Enamel hypoplasia Occ. conical crowns Occ. maloocl. (open-bite)
Hypohydrotic Ectodermal Dysplasia [13] (X-linked recessive)	Resembles inverted triangle Frontal bosses large	Alv. procc. absent Nasal root very depressed	Hypo- to anodontia Teeth present tend to be conical
Klippel-Feil Syndrome [14]	—	Cleft uvula or cleft palate High palate arch	—
Mandibulofacial Dyostosis [15] (structures from 1st branchial arch, groove, pouch)	(Fairly normal)	Malar very small often incompl. Hypoplastic mandible Palate high or cleft 40 per cent	Maloccl. freq. Occ. hypoplasia Space ++ Open bite freq.
Marfan's Syndrome [16] (autosomal dominant)	Dolichocephalic Frontal bosses large	Face long, thin Palate vault high Occ. cleft palate	Maloccl. frequent Teeth long, narrow
Morquio-Ullrich Syndrome [17]	—	Nasal bridge depressed Mild hypertelorism Palate high, long	Teeth have thin enamel Cusps flat, small
Oculomandibulo-dycephaly with Hypotrichosis [18]	Dycephaly, bulging skull Brachycephaly Prom. bosses Occ. platybasia	Hypoplastic mand. Face small Hypoplastic malar	Many teeth absent Malocclusion (open-bite) Occ. natal and supernumerary Occ. enamel hypoplasia
Orodigito-facial Syndrome [19]	Frontal bossing Steep ant. cranial base Occ. basilar kyphosis	Thin nose "Cleft" assoc. with hyperplasia of frenum Palate cleft laterally	Malposed C Supernum. C and P1–2 Aplastic I2

TABLE 2—*continued*

SYNDROME	SKULL	FACE	TEETH
Osteogenesis Imperfecta and Dentinogenesis Imperfecta, Clear (Blue) Sclerae, Otosclerosis, and Loose Ligg.[20] (as "hered. opalesc. dentin" is autosomal dom.)	Skull disproport. large Parietal bosses large	—	Dentin hit in 80 per cent decid., 35 per cent perm. Crown small Occ. premature eruption Roots short, thin
Progeria [21]	Head rel. large Prom. bosses	Face small, espec. mid-face Mand. hypoplasia Palate high, vault	Microdontia Eruption late Occ. hypodontia
Progressive Hemifacial Atrophy [22]	—	Asymmetrical face Corpus, ramus of mand. smaller on aff. side	Occ. late eruption on affected side

[1] Nanocephalic Dwarfism, Primordial Dwarfism, Ateliosis, Low-birth-weight Dwarfism, Intrauterine Growth Retardation.
[2] Mesoectodermal Dysplasia.
[3] Down's Syndrome, G Trisomy, Mongolism.
[4] Turner's Syndrome, Gonadal Dysgenesis or Agenesis, Ovarian-Short Stature Syndrome, Genital Dwarfism.
[5] "Chromatin-Positive Syndrome", Klinefelter's Syndrome, Gonadal Dysgenesis, Seminiferous Tubular Hyalinization with Gynecomastia, +Related Syndromes.
[6] Cleft Palate, Micrognathia and Glossoptosis.
[7] Freeman-Sheldon Syndrome, "Whistling-face" Syndrome.
[8] Crouzon's Syndrome, Hereditary Cranio-facial Dyostosis, Dyostosis Craniofacial (Crouzon), Maladie de Crouzon 1912, Morbus Crouzon 1912?
[9] Encephalofacial Angiomatosis, Encephalotrigeminal Angiomatosis, Meningofacial Angiomatosis, Sturge-Kalischer-Weber Syndrome, Sturge-Weber-Krabbe Syndrome, Congenital Neuroectodermal Dysplasia, Cutaneous Cerebral angioma, Angioma Capillare et Venosum Calcificans, Nevus Flammeus with Angiomatosis and Encephalosis Calcificans.
[10] Mucopolysaccharidosis I, Gargoylism, Hunter-Hurler-Pfaundler Syndrome, Dyostosis Multiplex.
[11] Grieg's Syndrome, Ocular Hypertelorism of Grieg, Hypertelorism (Grieg), Hypertelorismus Ocularis, Primary Embryonic Hypertelorism.
[12] Dysgenesis of Iris and Cornea, and Myotonic Dystrophy.
[13] Anhidrotic Ectodermal Dysplasia, Christ-Giemens-Touraine Syndrome, Weech's Syndrome.
[14] Brevicollis, Congenital Synostosis of Cervicothoracic Vertebrae, Congenital Osseous Torticollis.
[15] Treacher Collins' Syndrome, Franceschetti-Zwahlen-Klein Syndrome, Bilateral Facial Agenesis.
[16] Dolichostenomelia, Arachnodactyly, Dystrophia Mesodermalis Congenita.
[17] Osteochondrodystrophia Deformans, Morquio-Brailsford Syndrome, Hereditary Polytopic Enchondral Dysostosis, Infantile Hereditary Chondrodysplasia, Mucopolysacchardosis II.
[18] Dycephaly with Congenital Cataract and Hypotrichosis, Hallerman-Streiff Syndrome, Ullrich and Fremerey-Dohna Syndrome.
[19] Dysplasia Linguofacialis, OFD Syndrome.
[20] Ekman's Syndrome, Lobstein's Syndrome, Vrolik's Syndrome, Eddowe's Syndrome, Spurway's Syndrome, Adair-Dighton Syndrome, Fragilitas Ossium Syndrome, Osteopsathyrosis, Brittle Bones Syndrome.
[21] Hutchinson-Gilford Syndrome, Progeronanism.
[22] Romber's Syndrome, Parry-Romberg Syndrome, Progressive Facial Hemiatrophy, Facial Trophoneurosis.

Roentgenographic Cephalometer

For some thirty-five years the post-natal growth of the head, face and jaws has proceeded on a longitudinal basis via standard lateral head X-ray films, taken in a cephalostat (most often a Broadbent-Bolton Roentgenographic Cephalometer). The successive films are, by virtue of the standardized X-ray technique, so directly comparable that craniofacial details—both skeletal and soft tissue—may be traced, the tracings superposed, and by means of linear and angular relationships the serial tracings may be "analysed"

for growth and typological details. It is obvious that such a technique may lend itself to "patterning" and to family-line studies, and, in this manner to an evaluation of the transmissibility of possible heritable traits, be they dimensional (size) or angular (proportion), or a combination of both.

Wylie [146] made an early attempt in this direction. For parents and children he constructed on the lateral X-ray head films certain "facial polygons", the linear and gularan details of which were then compared. It was concluded as follows:

> None of the angles studied bears a relationship to any other angle in the craniofacial complex that is precise enough to be predictable. Furthermore, no definite relationship between any particular angle and any particular side of the polygon can be said to exist, and, finally, knowing that one particular side is relatively long or relatively short does not permit one to predict even roughly the length of the other side.

Lundstrom [97] also worked with lateral X-ray films, in MZ and DZ twins. He analysed the variance of cranio-facial linear and angular dimensions and relationships and demonstrated that the variability in DZ is twice as great as that in MZ. Sarnas [126] employed a similar technique in the analysis of inter- and intra-family variation in the facial profile. (Brown,[11] also did a parent-child study.) Analysis of variance showed, for example, "a higher degree of sib-likeness in the habitual rest position of the mandible with reference to the lower lip", while "upper and lower lip changes", while inter-correlated, have a lower degree of sib-likeness. Interestingly, Sarnas found that cranial base angles did not show "any mutual influence on the variation", while two corporo-ramal angles of the mandible were found to "influence the variation of each other". Similarly, the variability of anterior lower face height was influenced by the variability of the (vertical) over-bite.

Kraus, Wise and Frei [89] employed both lateral and frontal (p-a) X-ray head films. From these tracings they set up sixteen morphological "units" in the lateral X-ray film, one in the frontal X-ray film. The "hypothesis of genetic determination of the craniofacial complex" was tested on six sets of same-sex triplets, analysed into monovular and diovular pairs. From this study the authors concluded "that the morphology of all the bones of the craniofacial complex are under the rather rigid control of hereditary forces". Degrees of discordance are explained by the statement which follows: "It would seem that heredity governs morphology, but environment in its multitudinous facets has much to say about how these bony elements shall combine to achieve . . . the harmonious (or unharmonious) head and face".

Horowitz, Osborne and De George [75] studied the lateral X-ray head films of fifty-six pairs of like-sexed twins and found "very significant hereditary variations" in the anterior cranial base, mandibular corporal length, and total and lower face heights ($P<0{\cdot}001$). Upper face height is a more stable element in the facial profile, since it contributes little to the genetic variability of the face as a whole.

Prorok [116] used twenty-nine pairs of lateral X-ray head films as an aid to the determination of monozygosity in twins. He took, on the tracings, thirty-seven angular measurements and sixteen linear measurements. For the sixteen linear measurements "t" = 3·65, a significant difference between MZ and DZ pairs. The intra-pair error was 31 per cent., in differentiating MZ and DZ. For the angular measurements Prorok set up three groups of eleven each, according to cranial base lines of superposition (basion-nasion, Bolton-nasion, sella-nasion, resp.). The first eleven had a "t" = 4·16, error = 20·6 per cent; the second eleven a "t" = 4·42, error = 31 per cent; the third eleven a "t" = 4·89, error = 27·6 per cent. All thirty-seven angular measurements had a "t" = 5·36, error = 13·8 per cent. When the sixteen linear and the thirty-seven angular measurements were pooled the

TABLE 3
Resumé of hereditary traits

TRAIT	DOMINANT	RECESSIVE	SEX-LINKED
TEETH AND MOUTH			
1. *Teeth*			
Rate tooth develops	X(?)	—	—
Ant. teeth (I1–2)	X(?)	—	—
Very large $\underline{I1}$–$\underline{I1}$	X	—	—
Absence $\overline{I1}$	Inc. X	—	—
Absence $\overline{I2}$	X	X	X
Absence $\overline{Pm}$'s	X	—	—
Absence M's	X	—	—
Anodontia (w. hydrod.)	X	—	—
(w. anhydrod.)	—	—	X(R)
Carabelli's cusp	Intermed. X	—	—
Caries	X(?)	—	—
Defective enamel			
agenesis	—	—	XD
hypocalc.	X	—	—
hypomat.	—	—	XR
pig. hypomat.	—	X	—
loc. hypopl.	X	—	—
Dentin hypopl.	X	—	—
Dentinogen. imperf.	X	—	—
Diastemata	X	—	—
Shovel-shaped I	—	X	—
Supernum. teeth	X	—	—
Tooth size	X	—	—
2. *Oral cavity*			
Ankylgossia	X	—	—
Chondroect. dyspl.	—	X	—
Eruption pattern	X	—	—
Fibrous swell. jaws	X(?)	—	—
Ging. hyperplas.	X	—	—
Malocclusion (+ access. factors)	X(?)	X(?)	—
Progenia	X	—	—
Recessive chin	X(?)	—	—
Shape, size jaws	X(?)	—	(X, D?)
Torus mand, pal.	(X)	—	(XD)
JAWS AND FACE			
Cleft lip	(Inc.)	(X)	(X)
Cleft palate	X	—	—
Cleft palate+cleft lip	(Inc.)	(X)	+
Cleidocran. dysos.	X	—	—
Craniofac. dysos.	Irreg. X	—	—
Facial complex			
Size, shape	X	X	—
Dimensions	—	X?	—
Growth pattern	X	—	—
Hemiat.	—	X	—
Hemihypert.	—	X	—
Mand.-fac. dysos.	Irreg. X	—	—
Physiognom. traits			
Lip heights	X?	—	—
Thick upper ip	X	—	—
Thick lower lip	X?	—	—
Lower lip groove	X	—	—
Chin "clefts"	X	—	—

(*N.B.* This Table reflects both contradictory statements in the literature and recognition of a complexity that cannot yet be broken down. An example of the first is seen in "absence of I2", where D, R, and SL are all checked. An example of the second is malocclusion, where both D and R are checked, with a ? in recognition that in the total malocclusal complex it is impossible to be specific.)

"t" = 5·66, error only 10·3 per cent. The means of the MZ twin intrapair difference were only one-half those of the DZ twins intrapair differences.

Summary

1. The Reptilian-Mammalian evolutionary transition in face, jaws and teeth provides a structural, functional, selective and genetic framework for the concept of " fields" in the dental arches and in the dentition.

2. Twin, family-line and racial studies have demonstrated the possibility of many trait and trait-complexes in the human dentition which are under genetic control.

3. Similarly, tooth-size, whether considered individually, in functional quadrants, and in intra- and inter-arch relations, shows evidence of genetic control.

4. Structural defects in the teeth, especially involving the enamel and the dentin, are under genetic control.

5. The congenital absence of the teeth is mediated genetically. Especially is this true of $\frac{M3}{M3'}$, the agenesis of which has been shown to be a polymorphism; where M3 is absent there is a more frequent hypodontia. microdontia, and a slowed calcification and eruption. This polymorphic effect extends, in a degree, to the sibs of an affected child.

6. Tooth calcification and eruption, in sequence and in time, are under genetic control.

7. There is strong evidence that dental development is moderated by the same genetic mechanism that dictates maturation in general, and sex maturational differences in particular.

8. It is at present not possible to dichotomize between genetic and teratogenic effects in cleft lip and/or palate. It is likely that lip and primary palate cleft are largely genetic, while secondary palate cleft is largely teratogenic.

9. Caries susceptibility/immunity is too complex an entity to conclude more than that there may be (a) genetic factor(s).

10. The phenomena of tooth-bone inter-relationships during growth show evidence of polygenetic "patterning", as well as of syndromic association. This is borne out by serial analysis of facio-dental growth as observed roentgenographic cephalometrically. There are two main approaches via serial radiographic data: (1) The attempt to elucidate unit traits or functional loci; (2) An attempt to compare overall "pattern", i.e. the total cephalo-facial complex.

11. In Table 3 is presented a tabular summary of the data discussed in this review. Traits are listed under several categories. No attempt, in this tabulation, has been made to cite specific reference; for this the text must be carefully consulted.

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